3
Applications of Small-Molecule Gels – Drug Delivery

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3.1
Introduction

Gels are generally referred to as soft and versatile semi-solid materials which have inconspicuous presence in much of our daily lives. Depending on the nature of the material incorporated to form gels, they have wide application in various industries ranging from electronics, medical implants, and pharmaceutical delivery systems, to cosmetic usage and even in food. Owing to the various type of gels available, giving ''gel'' a clear definition has been a tacky task. It has been suggested that gel is defined as a soft, solid, or solid-like material of two or more components, one of which is a liquid present in substantial quantity [1]. A generally acceptable definition that has been proposed is that it is a semi-solid material composed of low concentrations of gelator molecules that, in the presence of an appropriate solvent, self-assemble into an extensive network mesh preventing solvent flow as a result of surface tension [2]. The three-dimensional networks, usually in the form of fibers, strands, or tapes, are held together by weak physical forces of attraction such as van der Waals interactions and hydrogen bonds to produce physical gels, while chemical gels are held together by stronger covalent bonds. Depending on the nature of the solvent used, gels formed with water as the liquid component are known as *hydrogels*, and gels that have organic solvent as the liquid component are known as *organogels*. Hydrogels have been extensively studied since about half a century ago, while the interest in organogels took off only in the last two decades.

Depending on the types of gelator used, the resulting hydro- or organogel can be further classified as a small-molecular-weight or polymeric gel. Small-molecular-weight gelators form a solid fiber matrix via permanent crystalline networks or a fluid fiber matrix via a noncovalent transient structural network that is constantly remodeling (Figure 3.1), thus making them thermoreversible. On the other hand, polymeric gels are made up of arrays of monomer units, ranging from linear to hyperbranched polymers, which solidify organic solvents through cross-links and covalent bonds (Figure 3.2) [2, 3]. Depending on the chemical properties of the gelators and solvent, as well as the conditions during gel processing, such as gelation temperature and rate of cooling, gels of different physiochemical properties can

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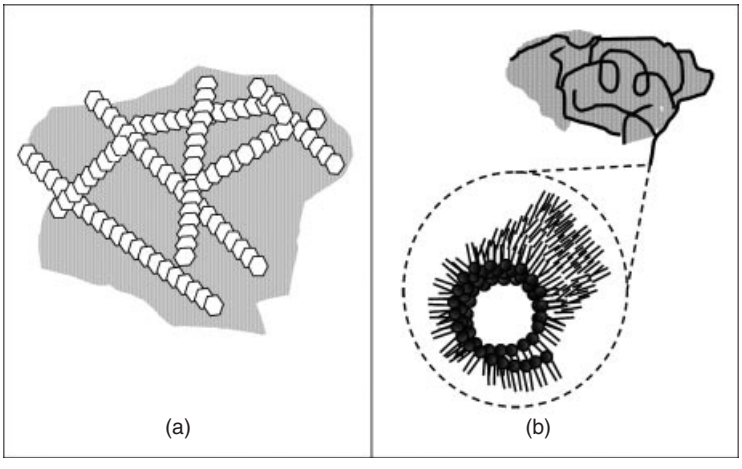

Figure 3.1 Schematic of small-molecular-weight organogelator networks. (a) Permanent crystalline linkage giving rise to solid fiber network. (b) Transient structural network of fluid fiber matrix formed by reverse micelles which enlarge cylindrically into an entanglement of dynamic lattice that immobilizes solvent to form a gel.

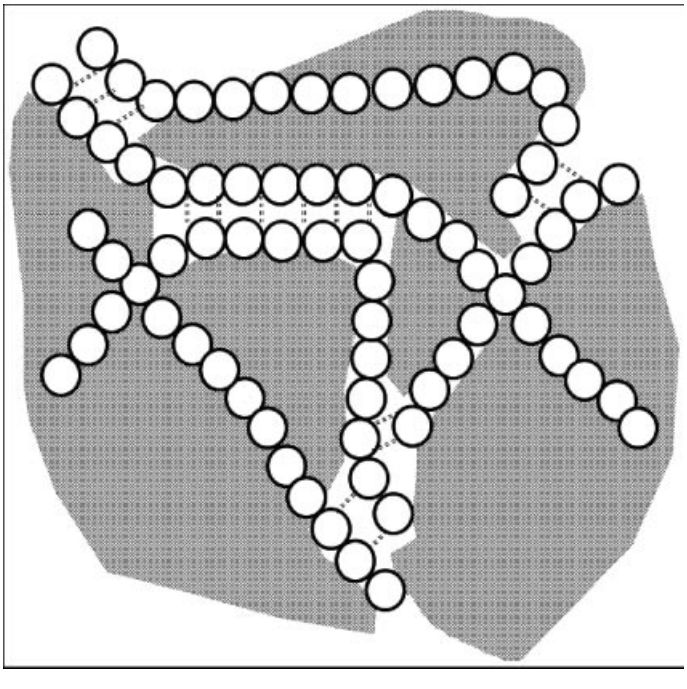

Figure 3.2 Schematic of polymeric organogelator network. Polymers self-assemble through non-covalent bonds and cross-links to form a three-dimensional network that holds organic solvent within and hence leads to gelation of the solvent.

be formulated to desired characteristics. Drug delivery using the microstructure network allows the entrapped drug molecules to be released from the gel matrix at a controlled rate over an extended duration. In addition, where local therapeutic effect is needed, a gel matrix drug delivery system has the advantage of maintaining localized high drug concentration.

Polymers are commonly used as gelators. However, only a handful of polymers are biodegradable *in vivo*, and concerns of toxicity from the degradation of polymers have limited the use of gels as drug delivery systems in pharmaceutical industries. The discovery and use of small-molecular-weight gelators of mass approximately less than 3000 in forming gels have sparked interest in recent years. Most gelators were found by chance rather than a planned design and the studies carried out thus far on most of these gelators have been focused mainly on the understanding of their chemical properties and rheology. More research is needed to explore and expand their applications in various fields. This review will focus mainly on the applications of small-molecular-weight gelators.

3.2 Hydrogels in Pharmaceutical Applications

Hydrogels are generally more biocompatible than organogels due to their high water content. They are commonly explored and used for various medical purposes ranging from contact lenses, *in situ* implants, tissue engineering, and regenerative medicine to drug delivery systems [4–10]. Emerging reports have shown encouraging development in the applications of hydrogels. However, the gelators used are mostly polymeric in nature, and hence the concerns regarding cytotoxicity from acute and chronic administration of polymers into the body are not resolved. The applications of small-molecular-weight hydrogels that have been reported to date are still scarce compared to small-molecular-weight organogels. There must be a balance between hydrophobic interactions and hydrogen bonds in the aqueous media to induce self-assembly and network formation of the small molecules to form hydrogels. Small-molecular gelling agents of aqueous solution have been categorized into four main classes: conventional amphiphiles, bolaamphiphiles, Gemini surfactants, and sugar-based systems. The examples of hydrogelators from these different classes have been well reviewed by Estroff and colleague [11].

3.2.1 Drug Carriers

The potential of small-molecular-weight gels as drug delivery vehicles for small drug molecules was illustrated by Friggeri and colleagues. Two quinoline derivatives, 8-aminoquinoline and 2-hydroxyquinoline, were entrapped within a thermoreversible and pH-sensitive hydrogel of *N,N′*-dibenzoyl-L-cystine [12]. It was found that the release of the drug molecules from the hydrogel was dependent on the interactions of the gelator with the drug molecules. Hence, a controlled drug

delivery hydrogel system is achievable with appropriate drug–gelator combinations and their concentration ratio. Vemula and coworkers had shown that it is possible to encapsulate a hydrophobic drug within the hydrophobic pockets of amygdalin derivatives hydrogel [13]. The model drug, curcumin was released upon addition of enzymes to trigger degradation of the hydrogel at physiological temperature. It was also illustrated that the rate of hydrogel degradation, and hence drug release rate, can be controlled by changing the enzyme concentration or temperature.

3.2.2
Drug-Derivatized Small-Molecular Hydrogelators

A number of investigators have reported the formation of hydrogels based on small-molecular gelators derivatized from known drug molecules for localized drug delivery. Xing *et al*. reported the synthesis of an antibiotic hydrogelator by adding a pyrene group to a vancomycin molecule [14]. The vancomycin-pyrene compound was able to initiate gelation at a concentration of 0.36% w/w without heating. Furthermore, the vancomycin-pyrene hydrogel was found to be 8- to 11-fold more potent against bacteria than the vancomycin molecule alone. It was proposed that the higher potency was due to elevated local concentration of the antibiotic analog on the bacterial surfaces. This was suggested to be due to binding of vancomycin hydrogelator to bacterial surfaces leading to further self-assembly of more drug molecules, and hence encapsulating the bacteria with an antibiotic-loaded hydrogel layer [14, 15]. This concept of derivatizing bioactive hydrogelator from drug molecules would be particularly useful in therapy for tumors where targeted high local drug concentration and minimal systemic side effects is sought after.

The encouraging example of derivatizing established small-molecular drug molecules into gelators hold promises in further development of existing drug application and delivery method. This will prompt pharmaceutical companies to relook into their current pool of pharmaceutical molecules, especially those with patent nearing expiry, for redevelopment opportunities.

3.2.3
Drug-Gelator Conjugates

A report by Yang *et al*. had shown the successful treatment of simulated uranium wounds in mice skins using hydrogels formed from self-assembly of a three-small molecules compound composing of two amino acid derivatives with anti-inflammatory properties and pamidronate which complexed with uranyl ions to reduce cellular toxicity [16]. Small-molecular hydrogelator with anti-inflammatory properties was also reported by Bhuniya and co-workers [17]. Their group synthesized the (S)-(+)-ibuprofen-based hydrogelator through peptide coupling reactions, producing a molecule with gelling abilities at concentration of 0.9% w/w in the presence of water. The gel formed is stable for several months. Due to the peptide linkage in the gelator, the drug-based hydrogel was easily degraded to release the drug through enzyme-mediated hydrolysis. In addition, it was demonstrated that

should structural modifications affect drug activities, gelation abilities, or enzyme activities restricted due to stereoelectronic effects, these problems may be overcome by linking the drug to the gelator through a self-immolating spacer molecule [18]. The specificity in enzyme-mediated activation of prodrug-gelator conjugates can be exploited for targeted delivery of drugs to specific sites. For example, a prodrug-gelator conjugate with peptide linkage specific for tyrosinase would be able to target melanoma where tyrosinase is present only in melanoma cells [19].

In another work also involving enzymes and supramolecular hydrogels, the research group utilized alkaline phosphatase to convert ionic group on an amino acid derivative to neutral group to form a small-molecular hydrogelator, which resulted in the formation of hydrogels [20]. The process uses enzymes for bond cleavage instead of formation reactions as mentioned earlier. Nonetheless the bond breaking reaction requires enzyme specificity, hence facilitates targeted delivery and site formation of supramolecular hydrogels. In a later work by the same investigator, application of enzyme-mediated formation of supramolecular hydrogels using phosphatase, thermolysin, and β-lactamase was further illustrated, which suggested new avenue for detecting activity of enzymes and screening for enzyme inhibitors [21].

3.3 Organogels in Pharmaceutical Applications

An organogel is easily prepared by warming a gelator in organic liquid until the solid gelator completely dissolves, and then cooling the solution to below the gelation transition temperature [22]. Small-molecular-weight organogelators have higher organogelation abilities than polymer organogelators. Various classes of small-molecular-mass gelators have been identified which include fatty acid derivatives, steroid derivatives, anthryl derivatives, amino acid-type, and organometallic compounds [22]. Some examples of small-molecular-weight and polymeric organogelators are listed in Table 3.1.

The pharmaceutical industry has taken increase interest in organogels due to the discovery of biocompatible organogelators in recent years. As compared to its hydrogel counterpart, organogels offer more as they are thermodynamically stable at ambient conditions and thermoreversible under suitable conditions. In addition,

Table 3.1 Examples of organogelators.

Small molecular weight	Polymeric
Lecithin [23–25]	Polylactide [26–30]
Sorbitan monostearate [31]	Polyethylene vinyl alcohol [32]
Glyceryl palmitostearate [33]	Polystearyl acrylate-acrylic acid [34]
Hydroxystearic acid [35]	

they are easily formed through spontaneous self-assembly of supramolecules and being organic in nature, are resistant to microbial contamination [2, 36]. Hence it accrues to desirable features of easy handling and longer product shelf-life for pharmaceutical formulations.

3.3.1 Dermal and Transdermal Formulation

Dermal and transdermal drug delivery is well accepted by patients as it is non-invasive and usually easily self-administered. From the pharmacological perspective, its effect is localized and hence has less systemic side effects. It is also an alternative route to oral administration for sustained and controlled of drugs which are readily metabolized by the liver to bypass the first-pass effect. Lecithin-based organogel as a vehicle for topical drug delivery have been well-studied [23–25]. Willimann and co-workers have illustrated that the lecithin organogel matrix is biocompatible, has low skin irritancy potential, can increase the solubility of drugs, and improve the transdermal transport rate of scopolamine across human skin *in vitro* [25]. In addition, an open vial of lecithin organogel is stable for at least one month at room temperature. Unfortunately, the skin is an effective natural barrier and hence development of transdermal drug delivery has been hindered. Chemical penetration enhancers have been deployed to modify the skin structure so as to increase its permeability. Many of these chemical penetration enhancers were found to be organogelators. The dual properties of these molecules unquestionably pave way for further development of organogels in dermal and transdermal drug delivery.

Our research group had previously investigated the application of small-molecular organogel in transdermal drug delivery of haloperidol, using an amino acid-type small-molecular-weight gelator, dibutyllauroylglutamide (GP1) in two solvents, isostearyl alcohol (ISA) and propylene glycol (PG) [37]. It was found that GP1 did not influence the drug permeation rate, but it increased permeation lag time. The *in vitro* human skin permeation study showed that drug permeation reached pseudo steady state faster in ISA-based gels than PG-based gels. In a separate study, we illustrated that the use of penetration enhancers improved transdermal drug delivery, through which we discovered that the incorporation of limonene into GP1/PG organogel was able to increase skin permeability, shorten lag time, facilitate delivery of drug *in vitro*, and enhance gel stability [38]. Further examinations of the physiochemical effects of terpenes on organogel for transdermal drug delivery illustrated that the oxygen-containing terpenes linalool and cineole decreased gel moduli and brittleness, and the reverse was observed for the hydrocarbon terpene, limonene [39]. It was proposed that linalool and cineole interfered with hydrogen bonding between GP1 molecules. On the other hand, limonene may have initiated a phase separation-mediated gelation, resulting in a change of the gel morphology. Although the terpenes altered the rheology, they did not significantly affect the chemical stability of the gels. Therefore, based on choice of terpenes, desired viscosity of small-molecular organogel with enhanced skin penetrating properties

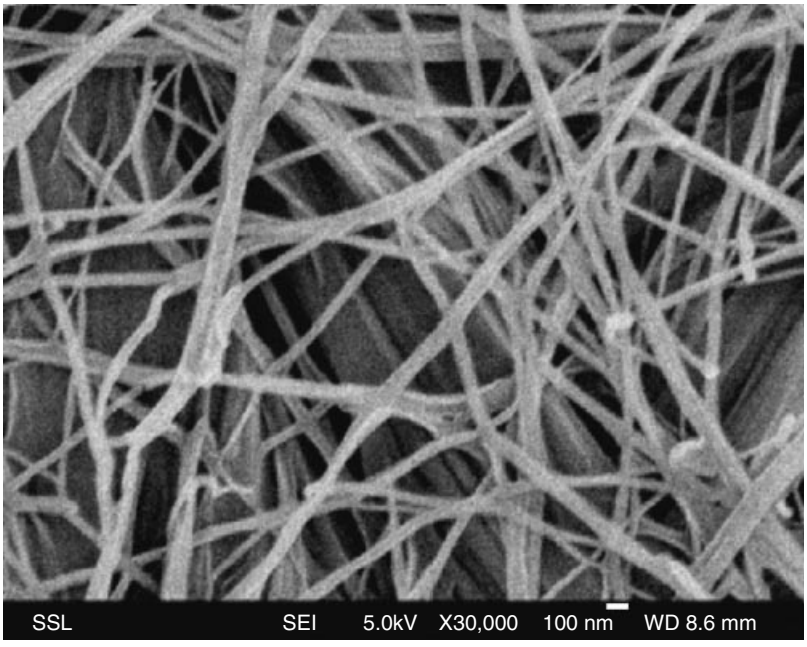

Figure 3.3 Fibrous network of GP1/PG organogel as viewed by scanning electron microscopy. Scale bar: 100 nm.

can be formulated without compromising the gel chemical stability. Furthermore, the GP1/PG organogel matrix (Figure 3.3) is easily prepared by mixing required amounts of components and heating without the need of any water.

Another modification of organogel to enhance dermal and transdermal drug delivery is the formulation of gelatin-stabilized microemulsion organogel using pharmaceutically acceptable surfactants and oil. Microemulsion-based organogel (MBG) is electrically conducting, and hence a higher drug release rate is observed when application is coupled with iontophoresis [40]. This encouraging result will open up new frontiers in transdermal delivery of larger molecules such as peptides and oligonucleotides.

3.3.2
Parenteral Depot Formulation

An injectable organogel drug delivery system has been used successfully in two pharmaceutical formulations, Eligard® [26–28] and Atridox® [29, 30]. Both formulations were based on the Atrigel® drug delivery platform, which is a biodegradable, liquid polymeric formulation composed of poly(DL-lactide) and *N*-methyl-2-pyrrolidone. The drug–polymer suspension solidifies into an organogel implant upon injecting into biological tissues, allowing localized controlled and sustained release of the drug over a period of time. Eligard® provides a depot of

leuprolide acetate for palliative treatment of advanced prostate cancer for a one-, three-, four-, or six-month treatment period, while Atridox® is used to deliver continuous doxycycline in the treatment of chronic periodontitis for a period of seven days. A promising result of injecting non-polymeric organogel was also seen in an *in vivo* evaluation of controlled release of contraceptive steroids from an organogel made up of polyglycolyzed apricot kernel oil and glyceryl palmitostearate [33]. It was demonstrated that the organogel *in situ* implant was effective in blocking the estrous cycle of rats for a prolonged period of 35 consecutive days as compared to 4 consecutive days in rats receiving oil formulation.

Recently, Bastiat and co-workers reported that an injectable organogel system based on safflower oil and *N*-behenoyl L-tyrosine methyl ester was able to deliver rivastigmine, an acetylcholinesterase inhibitor, for several weeks [41]. Hence, this preparation could possibly be an alternative treatment option for non-compliant patients with Alzheimer's disease. It has been reported that such an *in situ* forming implant is well tolerated and biocompatible [42–45]. The initial acute inflammatory response at the administered site is in line with the normal physiological immune response to foreign bodies and the wound healing process following injury. The inflammation and characteristic infiltrates would subside to a minimal level within two weeks [33, 41]. Furthermore, the shortcomings of burst effect and possibility of particulate migration to other sites as observed in microsphere delivery system were overcome by parenteral organogel formulation [46–50]. Moreover, the manufacture of a large-scale, reproducible and sterile organogel is much easier than the manufacture of a microsphere system [47, 48].

3.3.3 Oral Formulation

The concept of edible organogels has led to many potential applications in the nutraceutical and pharmaceutical industries, and even extends to technological improvements in food manufacture [51]. Organogels as an oral formulation offer the possibility of sustained and controlled release of lipophilic drugs. It was shown that when ibuprofen, a model lipophilic compound, was orally administered to rats in an aqueous suspension form, the ibuprofen concentration in plasma rapidly increased and then disappeared from the body. In contrast, when administered in an organogel formulation, the prolonged release from the gel matrix resulted in rapid absorption being suppressed, and t_{max} was significantly delayed, which synergistically enhanced the bioavailability of the ibuprofen [52]. Many lipid-soluble phytochemicals derived from plants are found to have therapeutic and health-promoting effects. However, beneficial effects of many of these bioactive compounds are not delivered to the patients simply because of low water solubility and poor bioavailability of the compounds. Yu and co-workers recently developed a food-grade organogel using monostearin, a GRAS (generally recognized as safe) organogelator, which achieved high bioaccessibility and loading of curcuminoids [53].

Application of orally administered organogel has been extended to a veterinary study, where chickens were vaccinated against Newcastle disease via raw rice

coated with trehalose organogels containing vaccine [54]. The organogel vaccine was stable and maintained an adequate infectivity titer after 12 weeks of storage at room temperature. Furthermore, a single-dose vaccine induced protective immune response in the chickens within four weeks. An orally administered organogel-based vaccine that is stable at room temperature has significant relevance where mass vaccination of population in underdeveloped countries is required. The ease of storage, transportation, and administration of such a vaccine is undeniably advantageous.

3.4
Organogel Delivery of Bioactive Factors in Regenerative Medicine

It has been shown that three-dimensional *in vitro* scaffolds are necessary to better mimic *in vivo* cellular behavior and interactions [55–57]. Roles of hydrogels as scaffolds in tissue engineering and cell cultures have been well explored [57–60]. Hydrogels provide for cells a three-dimensional scaffold that functions as an extracellular matrix enriched with biochemical factors and allows cell-to-cell interactions. On the other hand, studies on applications of organogels in tissue engineering have been scarce, mainly due to the limited availability of biocompatible organogelators and organic liquid. Recently Lukyanova and colleagues evaluated microporous organogel scaffolds made of the biocompatible and biodegradable ingredients soybean oil and capric/caprylic triglycerides with 12-hydroxystearic acid as gelator for cell viability and proliferation [35]. It was shown that soybean oil-based organogel scaffold with 7.5% w/w 12-hydroxystearic acid as gelator supported significant cell adhesion, growth, and proliferation. The porous organogel scaffold prepared by the particulate leaching method allowed distribution of nutrients and draining through the scaffold network, hence leading to cell growth and proliferation on both the surface and the internal structure of the scaffold during three weeks of culture. The discovery of this novel organogel scaffold will unleash the potential of delivering bioactive factors which may be favorable for cell culture and tissue engineering but which cannot currently be used due to hydrophobicity. In addition, the three-dimensional structure is more similar to the complex *in vivo* milieu then the conventional two-dimensional *in vitro* system, and consequentially it should result in a more accurate assessment of drug studies and cellular response.

3.5
Future Directions: Hybrid Organogels

The advantages and wide range of applications of organogels is well recognized. Besides the on-going work of discovering new gelators and organic solvents, another potential area for future research work is to incorporate micro- or nano-size particles into the organogels to produce hybrid organogels. The gel matrix can serve as a carrier and immobilize particles within a specific area for the

intended effect. Furthermore, hybrid organogels would allow hydrophobic and hydrophilic compounds to be harmoniously incorporated into separate particulate compartments within the same gel formulation. The benefit of a hybrid formulation is exemplified in dermal applications, where it translates to the ease of applying a single preparation for the combined therapeutic effects of otherwise incompatible gel preparations. In addition, hybrid organogel formulations will potentially provide a more sustained therapeutic effect, as drug compounds can be gradually released from the particles after the initial burst release from the gel matrix.

In actual fact, the ideology of hybrid organogels is not new. Murdan and co-workers experimented with organogels containing niosomes as a delivery vehicle for vaccine antigens more than a decade ago [31]. Light microscopy of their organogels prepared using the non-ionic surfactant sorbitan monostearate as the gelator showed a suspension of niosomes dispersed in a tubular network of surfactant aggregates. Model antigens, bovine serum albumin, and hemagglutinin were entrapped within the niosomes. Although immunogenicity studies showed that the niosomes-containing gels possess immunoadjuvant properties, they unfortunately did not elicit the expected higher antibody titers. This may be due to the low amount of niosome suspension in the gel, as well as the low entrapment efficiency of the niosomes during preparation.

An investigation into the role of an *in situ* implant that incorporates superparamagnetic iron oxide nanoparticles as a form of minimally invasive treatment of cancer lesions by magnetically induced local hyperthermia was recently carried out by Le Renard and co-workers [32]. *In vitro* and *in vivo* comparison studies were made among hydrogel, single-solvent organogel, and co-solvent organogel, which had concentrated single-solvent organogel diluted with low-toxicity hydrophilic solvent during gel preparation. It was found that the organogel formulations gave the most favorable result, where 8% poly(ethylene-vinyl alcohol) in dimethyl sulfoxide (DMSO) containing 40% w/v of magnetic microparticles formed the most suitable implants in terms of localization to tumor center and periphery, as well as heat delivery. Co-solvent organogels showed promising results and are clinically more appealing due to better safety profile than single-solvent organogels. However, high viscosity of the co-solvent formulations resulted in limited syringeability. It is hoped that further development will pave the way for clinical applications of magnetic microparticles-containing organogels in tumor treatments.

In recent years, characteristics of organogels with carbon nanotubes dispersed within the gel matrix have been studied [61, 62]. It was found that organogels containing 0.2% w/w of carboxylated nanotubes have increased mechanical strength by a factor of 4, and organogels with 0.2% w/w of pristine carbon nanotubes incorporated had electrical conductivity enhancement of 6 orders of magnitude [62]. This finding will have value in the development of fuel cells and energy. Presently, studies on hybrid gels are relatively limited. However, considering the benefits of using organogels alone and the potential extra advantages of using hybrid gels, research work in the area of hybrid organogels is expected to be favored in the future.

3.6 Conclusion

Small-molecular-weight hydro- and organogels are, without any doubt, versatile and multifunctional materials. New and different types of small-molecular gelling agents are constantly being reported. However, many of these reports do not include fully characterizing the new gelling agent [63–66]. More in-depth research in terms of applications would definitely widen the functional scope of small-molecular-weight gels and see their usage increase in various industries in the near future.

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